Research

Early-Life Environmental Exposures and Childhood Obesity: An Exposome-Wide Approach

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BACKGROUND: Chemical and nonchemical environmental exposures are increasingly suspected to influence the development of obesity, especially during early life, but studies mostly consider single exposure groups.

OBJECTIVES: Our study aimed to systematically assess the association between a wide array of early-life environmental exposures and childhood obesity, using an exposome-wide approach.

METHODS: The HELIX (Human Early Life Exposome) study measured child body mass index (BMI), waist circumference, skinfold thickness, and body fat mass in 1,301 children from six European birth cohorts age 6–11 y. We estimated 77 prenatal exposures and 96 childhood exposures (cross-sectionally), including indoor and outdoor air pollutants, built environment, green spaces, tobacco smoking, and biomarkers of chemical pollutants (persistent organic pollutants, metals, phthalates, phenols, and pesticides). We used an exposure-wide association study (ExWAS) to screen all exposure–outcome associations independently and used the deletion-substitution-addition (DSA) variable selection algorithm to build a final multiexposure model.

RESULTS: The prevalence of overweight and obesity combined was 28.8%. Maternal smoking was the only prenatal exposure variable associated with higher child BMI (z-score increase of 0.28, 95% confidence interval: 0.09, 0.48, for active vs. no smoking). For childhood exposures, the multiexposure model identified particulate and nitrogen dioxide air pollution inside the home, urine cotinine levels indicative of secondhand smoke exposure, and residence in more densely populated areas and in areas with fewer facilities to be associated with increased child BMI. Child blood levels of copper and cesium were associated with higher BMI, and levels of organochlorine pollutants, cobalt, and molybdenum were associated with lower BMI. Similar results were found for the other adiposity outcomes.

DISCUSSION: This first comprehensive and systematic analysis of many suspected environmental obesogens strengthens evidence for an association of smoking, air pollution exposure, and characteristics of the built environment with childhood obesity risk. Cross-sectional biomarker results may suffer from reverse causality bias, whereby obesity status influenced the biomarker concentration. https://doi.org/10.1289/EHP5975

Introduction

Rates of childhood obesity are increasing at alarming rates across the globe, with some leveling-off of this trend reported in Europe and high-income English-speaking regions [NCD Risk Factor Collaboration (NCD-RisC) 2017]. Greater body mass index (BMI) and adiposity in childhood are associated with future risk of type 2 diabetes, cardiovascular disease, certain cancers, lack of school achievement, and mental health problems (Park et al. 2012; Quek et al. 2017; Singh et al. 2008). Further, weight gained during childhood and adolescence is difficult to lose and likely to lead to adult overweight and obesity (Geserick et al. 2018). The primary cause of obesity is the imbalance between energy intake and energy expenditure (McAllister et al. 2009). Exposure to a wider range of environmental factors may influence this balance, either at the individual level by chemical exposures that influence metabolic programming, or at the community level by factors associated with the urban or built environment (Lichtveld et al. 2018; Trasande et al. 2009; Wilding et al. 2019).

At the individual level, a number of common chemical contaminants, including persistent organic pollutants, toxic metals, pesticides, tobacco smoke, and additives used in plastics and cosmetics, such as phthalates and phenols, may perturb adipogenesis and energy storage by interfering with the action of endogenous hormones, especially when exposure occurs *in utero* or during early life (Behl et al. 2013; Braun 2017; Janesick and Blumberg

2016; Thayer et al. 2012). Maternal exposure to ambient air pollution has convincingly been linked to reduced fetal growth and lower birth weight (Pedersen et al. 2013), and, as an extension, air pollution exposure during childhood may also be etiologically relevant to growth and the risk of obesity (Jerrett et al. 2014; Kim et al. 2018; McConnell et al. 2015). At the community level, built environment characteristics, such as walkability and green spaces, play a potential role in child physical activity habits and other health behaviors, and consequently in the development of childhood obesity, as childhood exposure studies have demonstrated (Gascon et al. 2016; Lachowycz and Jones 2011; Lichtveld et al. 2018; Saelens et al. 2018). One study has associated pregnancy traffic noise exposure, but not childhood exposure, with child BMI trajectories (Weyde et al. 2018). Further, in adults, ambient temperature and noise exposure have been linked to increased obesity risk, and exposure to ultraviolet (UV) radiation has been linked to reduced obesity risk (Gorman et al. 2017; Pyko et al. 2017; Voss et al. 2013).

Epidemiological studies on the early-life obesogenic effects of these environmental chemical and nonchemical stressors have almost exclusively assessed the risks of single-exposure families (Lichtveld et al. 2018), with the exception of a few multipollutants studies that included chemicals from three or four different exposure groups (Agay-Shay et al. 2015; Zhang et al. 2019). The exposome, described as "the totality of human environmental exposures from conception onward," recognizes that individuals are exposed simultaneously to a multitude of different factors and takes a holistic and agnostic approach to the discovery of etiological factors (Wild 2012). Even in its partial forms, the exposome provides a useful framework to systematically evaluate many associations (Wild 2012) and may be used to avoid problems of selective reporting, publication bias, and, to some extent, confounding by coexposures, ingrained in the typical one-by-one reporting of associations. Consequently, the exposome may help both in discovery and in setting priorities for prevention. Exposome-wide discovery approaches have recently been used to systematically assess many environmental exposures and reproductive and child health outcomes (e.g., lung function, semen quality, birth weight) (Agier et al. 2019; Chung et al. 2019; Nieuwenhuijsen et al. 2019).

In our study, we used an exposome approach to systematically assess the associations between a wide array of ubiquitous environmental exposures measured prenatally and during childhood with obesity indicators in children at primary school age.

Methods

Study Population

The HELIX (Human Early Life Exposome) project (Vrijheid et al. 2014) is a collaborative project across six established, ongoing, longitudinal population-based birth cohort studies in Europe: Born in Bradford (BiB) in the United Kingdom (Wright et al. 2013), Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) in France (Heude et al. 2016), INfancia y Medio Ambiente (INMA) in Spain (Guxens et al. 2012), Kaunas cohort (KANC) in Lithuania (Grazuleviciene et al. 2009), the Norwegian Mother and Child Cohort (MoBa) (Magnus et al. 2016), and the Rhea Mother Child Cohort in Greece (Chatzi et al. 2017). These cohorts contributed to the HELIX subcohort of z mother–child pairs who participated in a common, completely harmonized, follow-up examination between December 2013 and February 2016, when the children were between 6–11 y old, as fully described elsewhere (Maitre et al. 2018). Eligibility criteria for inclusion in the subcohort were: a) age 6–11 y at the time of the visit, with a preference for ages 7–9 y; b) sufficient stored

pregnancy blood and urine samples available for analysis of prenatal exposure biomarkers; c) complete address history available from first to last follow-up point; and d) no serious health problems that may affect the performance of the clinical testing or affect the volunteer's safety (e.g., acute respiratory infection). In addition, the selection considered whether data on important covariates (diet, socioeconomic factors) were available. Each cohort selected participants at random from the eligible pool in the entire cohort and invited them to participate in this subcohort until the required number of participants was reached. Our comparison of the subcohort with the entire group of cohorts (Maitre et al. 2018) showed that basic characteristics of the subcohort were somewhat different from those of the entire cohort, probably reflecting selective participation of families in the intensive subcohort follow-up visit and data completeness requirements. Compared with the entire cohort, the subcohort contained a greater percentage of boys, fewer children whose parents were born abroad, a lower percentage of mothers with low education, a lower percentage of primiparous mothers, and more older mothers. The work was covered by ethics approvals from each cohort, and all participants signed an informed consent form for the specific HELIX work, including clinical examination and biospecimen collection and analysis.

Environmental Exposures

We included 77 environmental exposures assessed during pregnancy and 96 exposures assessed during childhood at age 6–11 y (Table 1). The exposures were selected at the start of the HELIX project, because they were of concern for more than one of the health outcomes under study and because population exposure was widespread (Vrijheid et al. 2014). Some exposure variables available in the project (Tamayo-Uria et al. 2019) were not included in the current analysis for the following reasons: a) They had <30 subjects in one exposure category without possibility to recode [this was the case for diethyl dithiophosphate (DEDTP) in pregnancy and childhood, and dimethyl dithiophosphate (DMDTP) in pregnancy]. b) They had a correlation of 0.9 or higher with another similar variable of the same exposure group, in which case we selected one exposure variable representative for the group or a sum variable as described below under the specific exposures. c) They were calculated for several exposure time windows, in which case we included only the longest exposure window (e.g., pregnancy average instead of trimester averages).

Urban Environment

Urban environment exposures (built environment, surrounding natural spaces, meteorology, UV radiation, outdoor air pollution, traffic, and road traffic noise) were estimated as part of the HELIX project using geospatial models, monitoring stations, satellite data, and land use databases and were assigned to study participants according to their geocoded home and school addresses using GIS platforms [described in detail by Robinson et al. (2018), Nieuwenhuijsen et al. (2019), Tamayo-Uria et al. (2019)]. Sources of data for each exposure are summarized in Table S1. Exposures were averaged over the entire pregnancy (prenatal exposures) and over the year before the child examination (childhood exposures), with the exception of UV radiation and meteorological variables (temperature, humidity), which were averaged over the month before the child examination. If the family moved during those periods, exposures were calculated for each address and then averaged over the period (pregnancy, year before child examination).

Table 1. Exposure variables included in the prenatal and childhood exposome.

Exposure group	Exposure assessment method	Exposure variables	Number of variables	
Built environment	GIS linkage to local or Europe-wide maps (Table S1)	Population density (inhabitants per km²), street connectivity (number of road intersections per km²), building density (built area in m² per km²), accessibility with bus public transport (meters of bus lines and number of bus stops), facility richness (pregnancy only[a]) and facility density, Land Use Evenness Index and walkability index, each within a 300-m buffer. Home and school address during pregnancy. Home and school address during childhood (walkability only home). All using buffer of 300-m.	9	15
Surrounding natural spaces	GIS linkage to satellite images and local or Europe-wide maps (Table S1)	Average Normalized Difference Vegetation Index (NDVI) within buffer of 100 m; presence of a major green space in a distance of 300 m; presence of a major blue space in a distance of 300 m. Home address during pregnancy. Home and school address during childhood.	3	6
Meteorology	GIS linkage to local weather station data (Table S1)	Temperature, humidity, pressure at home address. Pressure only available during pregnancy. Averaged over pregnancy and month before visit during childhood.	3	2
Ultraviolet (UV)	GIS linkage to satellite measurements	Ambient UV radiation levels at home address. Averaged over month before visit during childhood. Not included in pregnancy.[b]	0	1
Outdoor air pollution	GIS linkage to existing local land-use regression models from the ESCAPE project or dispersion models (Table S1). Temporal adjustment using local monitoring data.	NO_2, $PM_{2.5}$, PM_{10}, $PM_{2.5abs}$ at home address. Averaged over pregnancy and year before visit in childhood.	4	4
Traffic	GIS linkage to local road network maps (Table S1)	Total traffic load of roads in a 100-m buffer (pregnancy and childhood home address), total traffic load of major roads in a 100-m buffer (childhood home and school), traffic density on nearest road (pregnancy and childhood home), and inverse distance to nearest road (pregnancy and childhood home).	3	5
Road traffic noise	GIS linkage to municipal noise maps (Table S1)	24-hour road noise levels (pregnancy, and childhood home and school address). Nighttime noise levels for home during childhood.	1	3
Indoor air pollution	Newly development prediction models based on indoor measurements and questionnaire data	NO_2, TEX, Benzene, PM_{10}, $PM_{2.5abs}$	0	5
Tobacco smoking	Questionnaires and biomarker measurement of cotinine	Urine concentration of cotinine (pregnancy and childhood[c]), active/secondhand smoking during pregnancy, number of cigarettes during pregnancy, parental smoking, and secondhand smoking during childhood.	3	3
Organochlorine compounds (OCs)	Biomarker measurement	Blood concentrations of DDE, DDT, HCB, PCB (118, 138, 153, 170, 180), and sum of the PCBs	9	9
Polybrominated diphenyl ethers (PBDEs)	Biomarker measurement	Blood concentrations of PBDE47, PBDE153	2	2
Perfluoroalkyl substances (PFAS)	Biomarker measurement	Blood concentrations of PFOA, PFNA, PFUnDA, PFHxS, PFOS	5	5
Metals and elements	Biomarker measurement	Blood concentrations of As, Cd, Co, Cs, Cu, Hg, Mn, Mo, Pb, Tl	10	10
Phthalate metabolites	Biomarker measurement	Urine concentrations of MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, OHMiNP, OXOMiNP, and sum of DEHP metabolites[c]	11	11
Phenols	Biomarker measurement	Urine concentrations of MEPA, ETPA, BPA, PRPA, BUPA, OXBE, TRCS[c]	7	7
Organophosphate (OP) pesticide metabolites	Biomarker measurement	Urine concentrations of DMP, DMTP, DMDTP (childhood only), DEP, DETP[c]	4	5
Water disinfection by-products (DBPs)	Existing prediction models from the HiWATE project based on routine water DBP measurements	THM, chloroform, brominated THMs tap water concentrations (pregnancy only)	3	0
Social and economic capital	Questionnaires	Family affluence score, social contact with friends and family, social participation in organizations	0	3
Total			77	96

Note: As, arsenic; BPA, bisphenol A; BUPA, N-butyl paraben; Cd, cadmium; Co, cobalt; Cs, cesium; Cu, copper; DBP, disinfection by-products; DDE, 4,4′dichlorodiphenyl dichloroethylene; DDT, 4,4′dichlorodiphenyltrichloroethane; DEP, diethyl phosphate; DEHP, di(2-ethylhexyl) phthalate; DETP, diethyl thiophosphate; DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; DMDTP, dimethyl dithiophosphate; ETPA, ethyl paraben; HCB, hexachlorobenzene; Hg, mercury; MBzP, mono benzyl phthalate; MECPP, mono-2-ethyl 5-carboxypentyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MEPA, methyl paraben; MiBP, mono-iso-butyl phthalate; Mn, manganese; Mo, molybdenum; MnBP, mono-n-butyl phthalate; NO_2, nitrogen dioxide; OHMiNP, mono-4-methyl-7-hydroxyoctyl phthalate; OP, organophosphate; OXBE, oxybenzone; OXOMiNP, mono-4-methyl-7-oxooctyl phthalate; Pb, lead; PBDE153, 2,2′,4,4′,5,5′-hexa-bromodiphenyl ether; PCB, polychlorinated biphenyl –118, 138, 153, 170, 180; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of less than 10 μm; $PM_{2.5abs}$, absorbance of PM_{10} filters; PRPA, propyl paraben; TEX, toluene, ethylbenzene, xylene; Tl, thallium; THM, trihalomethanes; TRCS, triclosan.

[a]Excluded from prenatal exposome due to very high correlation with temperature ($r > 0.9$).

[b]Excluded from childhood exposome due to very high correlation with facility density ($r > 0.9$).

[c]During childhood, the urine sample analyzed was a pool of equal amounts of two spot urine samples collected at bedtime the day before and in the morning on the day of the clinical examination.

Built environment factors were calculated from topological maps obtained from local authorities or from Europe-wide sources. Buffers of 100 and 300 m were used, but in this study only the 300-m buffer estimates were included due to the high correlations between variables. Building density was calculated within the 300-m buffer by dividing the area of building cover (m^2) by the area of the buffer (km^2). Population density was calculated as the number of inhabitants per square kilometer surrounding the home address. Street connectivity was calculated as the number of street intersections inside the 300-m buffers, divided by the area (km^2) of the buffer. A facility richness index was calculated as the number of different facility types present divided by the maximum potential number of facility types specified, in a buffer of 300 m, giving a score of 0 to 1. Facilities included businesses, community services, educational institutions, entertainment, financial institutions, hospitals, parks and recreation, restaurants, shopping, and transport (Smargiassi et al. 2009; European Environmental Agency 2010). A facility density index was calculated as the number of facilities present divided by the area of the buffer (number of facilities/km^2). Due to the high correlation between facility richness and density ($r > 0.9$) in the childhood exposure data set, only facility density was retained. Land use Shannon's Evenness Index (SEI) was calculated to provide the proportional abundance of each type of land use within the buffer, giving a score between 0 and 1 (Shannon 2001). It was calculated by multiplying each proportion of land use type by its logarithm and dividing the sum of all land use type products by the logarithm of the total possible land use types. We developed an indicator of walkability, adapted from the previous walkability indices (Duncan et al. 2011; Frank et al. 2006; https://www.walkscore.com), calculated as the mean and sum of the deciles of population density, street connectivity, facility richness index, and land use SEI within 300-m buffers, giving a walkability score ranging from 0 to 1. Accessibility was measured by bus public transport lines (meters of bus lines inside the buffer) and stops (number of bus stops inside the buffer), using maps from local authorities and OpenStreetMap® (https://www.openstreetmap.org/#map=4/38.01/-95.84) (Table S1).

Surrounding natural space indicators included the Normalized Difference Vegetation Index (NDVI) and presence of major green and blues spaces. The NDVI was used to measure surrounding vegetation (trees, shrubs, and park) (Weier and Herring 2000) and calculated following the protocol developed in the Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe (PHENOTYPE) study (Nieuwenhuijsen et al. 2014). Satellite images were derived from the Landsat 4–5 TM, Landsat 7 ETM+, and Landsat 8 OLI/TIRS satellites with 30 m × 30 m resolution. We selected images for 1 y relevant to the pregnancy period and for 1 y relevant to the subcohort follow-up, according to the following criteria: *a*) cloud cover less than 10%; *b*) Standard Terrain Correction (Level 1T); and *c*) greenest period of the year. This study uses the 100-m buffer for NDVI. The presence of major green spaces (parks or countryside) or blue spaces (bodies of water) was calculated by dichotomous variables, which indicate whether a major (area greater than $5,000\,m^2$) green/blue space was present or not within a 300-m buffer from Europe-wide or local topographical maps (Table S1) (Smargiassi et al. 2009; European Environmental Agency 2010).

Meteorological variables were calculated using daily measures of temperature and humidity obtained from local weather stations in each study area. Pressure data were obtained from the ESCAPE project (Giorgis-Allemand et al. 2017), and were available only for the pregnancy period. In this study, we used values averaged over the pregnancy period and over the month before

the subcohort visit, and we used childhood exposure calculated for the home, not the school, address.

UV radiation was estimated from daily measurements of ultraviolet (UV) radiation obtained from the Global Ozone Monitoring Experiment on board the European Remote Sensing satellite 2 (ERS-2) (http://www.temis.nl/uvradiation/archives) at $0:5 \times 0:5$-degree resolution. These were averaged over the month before the subcohort visit and were not available during pregnancy.

Outdoor air pollution estimates were calculated for nitrogen dioxide (NO_2), particulate matter with an aerodynamic diameter of less than 2.5 μm (PM_{10}) and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), as well as absorbance of PM_{10} filters ($PM_{2.5abs}$—a marker of black/elemental carbon originating from combustion). As part of the HELIX study, exposure estimates were calculated using existing land use regression models developed in the context of the ESCAPE project (Beelen et al. 2009, 2013; Cyrys et al. 2012; Eeftens et al. 2012a, 2012b; Schembari et al. 2015; Wang et al. 2014), except the EDEN cohort [where we applied existing NO_2 and PM_{10} dispersion models developed specifically for that cohort (Rahmalia et al. 2012)] (Table S1). These estimates were temporally adjusted to measurements made at the local background monitoring stations and averaged over the periods of interest for the HELIX study. Back-extrapolation based on other available pollutants was used when data on a pollutant were not available. In particular, daily PM_{10} was used to adjust NO_2; daily NO_2 or PM_{10} to adjust PM_{10}; daily NO_2 to adjust PM_{10}; and daily NO_x to adjust $PM_{2.5abs}$.

Traffic density indicators were calculated from road network maps following the ESCAPE protocol (Beelen et al. 2013; Eeftens et al. 2012a), using a 100-m buffer. For Rhea, a fieldwork campaign was conducted in Heraklion in 2015 to assess multiple exposures, including traffic, as previously described (van Nunen et al. 2017). For the analyses in this paper, we selected the total traffic load on all roads, the traffic density on nearest road, and inverse distance to nearest road for the pregnancy and childhood home address, as well as the total traffic load on major roads for the childhood home and school address.

Noise levels were derived from noise maps produced in each local municipality under the European Noise Directive (Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and management of environmental noise 2002) calculated as the annual average sound pressure level of a 24-h period (day, evening, and night) with a 5-dB penalty for evening noise (1900–2300), and a 10-dB penalty added to nighttime noise (2300–0700), and the annual average sound pressure level of the night period. Values were categorized into four categories (<55; 55–59.9; 60–64.9; and >65) for analysis. For Rhea, estimates on noise were newly modeled following the new fieldwork campaign in 2015, which gave a model R^2 of 45% (van Nunen et al. 2017). We included the annual average of noise levels of 24-h periods during pregnancy and during childhood for the home and school address, as well as the annual average of nighttime noise levels during childhood for the home address.

Indoor Air Pollution

Indoor air concentrations of NO_2, PM_{10}, $PM_{2.5abs}$ and benzene, as well as toluene, ethylbenzene, xylene (TEX) were estimated through a prediction model that combined measurements in the homes of a subgroup of children with questionnaire data from the subcohort. Measurements of indoor NO_2, benzene, and TEX were conducted in the living rooms of the homes of 157 children from the subcohort (12%) for 1 wk in two seasons using passive samplers. The TEX variable was created by summing the concentrations of each TEX compound. PM_{10} and $PM_{2.5abs}$ were

measured in 92 homes (7%) for 24 h in two seasons using active PM_{10} cyclone pumps. Details of the sampling methods are described elsewhere (Tamayo-Uria et al. 2019). Housing and participant characteristics for input into the prediction model were selected from the main HELIX subcohort questionnaire, which asked about characteristics of the current residence (Maitre et al. 2018). These characteristics included secondhand smoke (SHS), cooking and heating methods at the home, cleaning products, outdoor NO_2, presence of a garage connected to the house, and calendar month (Table S2). The variables that yielded a p value lower than 0.2 in bivariate analyses (Kruskal-Wallis or Wilcoxon rank sum tests) were selected into a multivariable linear regression model. A supervised forward stepwise procedure was employed to build multivariable linear regression models, starting with the variable that yielded the highest adjusted R^2 in bivariate models and then adding other predictors one by one until none of the variables increased the adjusted R^2 by more than 1%. R^2 values for the prediction models were 57% for NO_2, 50% for $PM_{2.5abs}$, 47% for PM_{10}, and 31% for benzene and TEX (Table S2). These prediction models were then used to estimate these five indoor air pollutants in the entire subcohort.

Tobacco Smoking

Tobacco smoking was assessed during pregnancy and childhood based on urine concentrations of cotinine (see below), and via questionnaires for active and secondhand smoking. Questions on tobacco smoking during pregnancy were harmonized across the cohorts. Maternal tobacco smoking at any point during pregnancy was placed one of in three categories: no exposure, only SHS exposure, and active smoking. Active smoking was also measured by the number of cigarettes per day on average during pregnancy. Childhood exposure to SHS was based on two variables: *a*) overall exposure of the child to SHS with two categories ["no exposure" (no exposure at home nor in other places) and "exposure" (exposure in at least one place, at home or outside)]; and *b*) active smoking of the parents ("1" neither parent, "2" one parent, or "3" both parents). For maternal cotinine levels during pregnancy, a categorical variable was created based on the urine concentration of cotinine distinguishing nonsmokers [values below the limit of detection (LOD) or cotinine levels <18.4 μg/L], secondhand tobacco smokers (cotinine levels ≥18.4 and ≤50 μg/L), and smokers (cotinine levels >50 μg/L) (Sunyer et al. 2012). In the children, a categorical variable was created categorizing urinary cotinine levels as detected or not detected considering the limit of detection of 3.03 μg/L.

Chemical Exposures

Exposure to chemical pollutants [organochlorine compounds (OCs), polybrominated diphenyl ethers (PBDEs), perfluoroalkyl substances (PFAS), metals and elements, phthalate metabolites, phenols, organophosphate (OP) pesticide metabolites, and cotinine] was measured as part of the HELIX project in biological samples collected previously by the individual cohorts during pregnancy, and in samples newly collected from the children during the common HELIX subcohort follow-up at age 6–11 y (Table 1). Details on the sample selection, laboratory methods, limits of quantification, LOD and quality control, including inter-lab comparison for already analyzed maternal samples, are fully described in Haug et al. (2018).

Maternal samples used to measure pregnancy exposures were those stored in the cohort biobanks, including: plasma and serum to measure OCs and PBDEs; plasma, serum, and whole blood to measure PFAS; whole blood and cord blood to measure metals and elements; and spot urine samples for all other compounds (see

sample matrix in Table S3). Measurements of maternal samples were performed at the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH) in Norway, or in the case of metals and cotinine, in collaboration with their contract laboratories. Measurements had already been completed for some compounds in INMA (OCs, PFAS, mercury, phthalate metabolites, cotinine (Aurrekoetxea et al. 2013; Goñi et al. 2007; Manzano-Salgado et al. 2015; Ramon et al. 2011; Valvi et al. 2015), EDEN (phenols) (Philippat et al. 2011), and Rhea [OCs; 2,2′,4,4′-Tetrabromodiphenyl ether (PBDE47)] (Koponen et al. 2013). These measurements were not repeated in HELIX, and instead the results were made available for this study and were used in statistical analyses (Table S4). Because different samples matrices were used for the analyses of maternal samples, some conversion factors were applied (Haug et al. 2018). For OCs and PBDEs, the concentrations in serum and plasma were assumed to be comparable (1:1 ratio) (Grimvall et al. 1997); for the PFAS, 1:1 ratios were assumed for serum and plasma, and 1:2 ratios were used for whole blood vs. serum/plasma (Poothong et al. 2017), multiplying all whole-blood concentrations by two; finally, cord-blood mercury concentrations were divided by 1.7 to be comparable with maternal whole-blood concentrations (Stern and Smith 2003).

The sample collections for the children were performed in a completely harmonized way, using the same protocols and equipment for sample collection and processing in all the six cohorts (Maitre et al. 2018). OCs and PBDEs were measured in serum, PFAS in plasma, metals and elements in cord blood, and all other compounds in urine (see Table S3 for sample matrix). The urine sample analyzed was a pool of equal amounts of two spot urine samples collected at bedtime the day before and in the morning on the day of the clinical examination. The children's samples were randomized into batches before chemical analyses, aiming at a minimum of three cohorts to be included in each batch. As with the maternal samples, the child samples were analyzed at the NIPH in Norway, or, in the case of metals and cotinine, in collaboration with their contract laboratories.

For all determinations conducted by NIPH or their contract laboratories, concentrations were reported below the limit of quantification (LOQ) whenever a signal was observed on the instrument. These results were used. For samples where no concentrations had been generated (concentrations below LOD), individually imputed values were obtained using a quantile regression approach for the imputation of left-censored missing data implemented in the imputeLOD function available in the rexposome package in the R software (version 3.4.0; R Development Core Team (Jin et al. 2011).

Concentrations of OCs and PBDEs were adjusted for serum lipid concentrations; phthalate metabolites, phenols, OP pesticide metabolites, and cotinine were adjusted for urinary creatinine. High correlations coefficients (>0.9) were observed for correlations within the individual polychlorinated biphenyl (PCB) congeners and within the individual metabolites of bis(2-ethylhexyl) phthalate (DEHP). For these, sum variables were created to combine the individual compounds into one variable. We then used the individual variables in single exposure models and sumPCB and sumDEHP variables in multiple exposure models (see below).

Water Disinfection By-Products

Routine measurements of disinfection by-product (DBP) concentrations in tap water were collected from water companies for all the cohorts for the pregnancy period, as described in detail in Tamayo-Uria et al. (2019). For KANC, BiB, INMA, and Rhea, we used the water DBP concentrations obtained for these cohorts

as part of the HiWate project (Jeong et al. 2012). As part of HELIX, routine water DBP measurements were acquired for MoBa and EDEN. Water trihalomethane (THM) exposure levels were then modeled for each residence, following the protocol developed in HiWate, which predicted average THM levels from conception until delivery for each participant's residential water supply (Jeong et al. 2012). We estimated exposure to total water THMs, and for water chloroform and water brominated THMs, and used the pregnancy average herein.

Social and Economic Capital

Questions related to social capital were included in the HELIX questionnaire to capture different aspects of social capital, relating both to the cognitive (feelings about relationships) and structural (number of friends, number of organizations) dimensions and to bonding capital (close friends and family), bridging capital (neighborhood connections, looser ties), and linking capital (ties across power levels; for example, political membership). Two summary variables were selected for the exposome analysis: social participation (membership of organizations: 0, 1, or 2) and contact with friends and family (daily, once a week, less than once a week). We also calculated the Family Affluence Score (FAS) as a measure of the family's economic capital, with levels low (score = <2), middle (score 3–5), and high (score > = 6) (Boyce et al. 2006; Liu et al. 2012). The FAS was calculated based on the responses to four items: *a*) Does your family own a car, van or truck? *b*) Do you have your own bedroom for yourself? *c*) During the past 12 months, how many times did you travel away on holiday with your family? *d*) How many computers does your family own?

The exposure levels and distributions of each exposure variable are described elsewhere (Tamayo-Uria et al. 2019) as are the correlation patterns between exposure variables (Haug et al. 2018; Robinson et al. 2018; Tamayo-Uria et al. 2019). In our supplemental material we provide the correlation matrix for prenatal and childhood exposure variables (Supplemental Excel Files Table E1 and E2).

Childhood Obesity Outcomes

During the subcohort examination at age 6–11 y, height and weight were measured using regularly calibrated instruments and converted to BMI age-and-sex–standardized z-scores (zBMI) using the international World Health Organization (WHO) reference curves (de Onis et al. 2007). Children who were overweight and obese were defined as those above the age-and-sex–standardized z-scores 1 and 2, respectively, as recommended by the WHO (de Onis and Lobstein 2010; de Onis et al. 2007). We measured waist circumference as an indicator of visceral fat in duplicate to the nearest 0.1 cm in a standing position, at the high point of the iliac crest at the end of a gentle expiration, with the use of a measuring tape (Seca 201; Seca Corporation). Skinfold thickness was measured at two anatomic sites (subscapular and triceps) on the right side of the body in triplicate to the nearest 0.1 mm with a calibrated caliper following the protocols from the National Health and Nutrition Examination Survey III (NHANES III Body Measurements 1988). We then calculated the sum of these two skinfolds as an index of subcutaneous fatness. Bioelectric impedance analyses were performed with the Bodystat 1500 (Bodystat Ltd.) equipment after 5 min of lying down. The proportion of fat mass was calculated using published age- and race-specific equations validated for use in children (Clasey et al. 2011). For all measures, we used common standardized protocols and the same instruments across the cohorts. For waist circumference, skinfold thickness, and proportion fat mass,

we calculated age-and-sex–standardized z-scores using the distribution of the full study population combining all cohorts.

The outcomes were correlated, with correlation coefficients between 0.59 (between overweight and obesity status and fat mass) and 0.79 (between zBMI and waist circumference z-scores). Our main analyses focused on zBMI and overweight and obesity status, to ensure comparability with existing literature, and the other outcomes were included to evaluate consistency of results.

Covariates

Information on key covariates was collected during pregnancy and in the subcohort follow-up examination and included maternal sociodemographic variables, maternal prepregnancy zBMI, maternal diet, maternal physical activity, birth weight, breastfeeding duration, child physical activity, child sleeping patterns, and the Mediterranean diet quality index (KidMed) questionnaire (Serra-Majem et al. 2004). The KidMed index consists of 16 questions, with questions denoting a negative connotation with respect to the Mediterranean diet assigned a value of −1 and questions with a positive aspect scored +1. In children, a "moderate-to-vigorous physical activity" variable was created based on the HELIX questionnaire data to define the amount of time children spent doing physical activities with intensity above three metabolic equivalent tasks (METs). Physical activity overreporting was corrected based on the correlation between accelerometer data (Actigraph) and questionnaire answers, using data from three nested panel studies in which participants wore accelerometers for 2 nonconsecutive wk (Maitre et al. 2018). Sleep duration in childhood corresponded to the average sleep duration at night during an entire week (weighted average of weekdays and weekend sleep duration). This variable was calculated based on the questionnaire taking the average bedtime and wake-up time (earliest and latest bedtime and wake-up times available) during weekdays and weekends. The questionnaire asked about usual sleep patterns.

Statistical Analysis

Skewed exposure and covariate variables were transformed to achieve normality; when normality could not be achieved with a transformation, the variable was categorized. Missing values for all exposures and covariates were imputed using the method of chained equations (White et al. 2011), as described in detail elsewhere (Tamayo-Uria et al. 2019). Twenty imputed data sets were generated to take into account the uncertainty resulting from the imputation. After imputation, continuous exposure variables were standardized by the interquartile range (IQR). In all subsequent regression models, Rubin's rules were used to combine the results from the 20 imputed data sets (White et al. 2011). We used linear regression models for the four continuous outcome variables (zBMI, z-scores of waist circumference, skinfolds, and fat mass) and logistic regression models for overweight and obese status. All analyses were applied separately to the set of prenatally measured exposures and the set of childhood exposures. We followed a two-tiered analysis strategy, based on our earlier methodological work (Agier et al. 2016):

ExWAS (exposure-wide association study) as a screening analysis of single exposures. We first estimated associations with each exposure variable individually using independent regression models. To account for multiple comparisons, a family-wise error rate correction was used to correct the p-value threshold (5% divided by the effective number of tests) (Li et al. 2012); the multiple testing corrected p-value thresholds were 0.001 for prenatal exposures and 0.0009 for childhood exposures.

DSA (deletion/substitution/addition) algorithm. Subsequently, we used the DSA variable selection algorithm to select a reduced number of statistically significant exposures, each adjusted for the other exposures (Sinisi and van der Laan 2004); this resulted in our final multiexposure model. We selected the DSA algorithm as our main analysis because it showed better model selection efficiency, in particular a lower false positive rate, in comparison with other linear regression-based methods, including ExWAS, in our simulations of a similar exposome data set (Agier et al. 2016).

The DSA method is an iterative process that starts with an empty model and uses deletion (removing variables from those selected), substitution (replacing selected variables by unselected ones), or addition (selecting new variables) to select a final model by minimizing the value of the root mean squared error of predictions using 5-fold cross-validated data. Cross-validation results were stabilized by fitting the DSA 50 times on the data using different seeds, and exposures were retained in a final multiexposure regression model if they were selected in at least 10% of the DSA runs. In the final multiexposure models we checked whether any exposure variables showed evidence for multicollinearity with other exposure variables. In this case, the variable with the most stable results compared with the ExWAS single exposure model was included in the final model. In our analysis, multicollinearity occurred only for 2,2′,4,4′,5,5′-Hexabromodiphenyl ether (PBDE153) and PBDE47, and PBDE47 was excluded from the final childhood multiexposure models. We applied DSA to the 20 imputed data sets stacked one after the other using weights (Wood et al. 2008), allowed no polynomial or interaction terms, and considered models including up to 25 covariates.

All above regression models were adjusted for a common set of potential confounders, decided on the basis of a Directed Acyclic Graph (Figure S1), which included: sex, cohort, maternal education level (low, middle, high), maternal age (continuous), maternal prepregnancy BMI (continuous), parity (nulliparous, primiparous, multiparous), and parental country of birth (both parents native, none or one native parent). In the childhood exposure models, we also included birth weight and breastfeeding duration as adjustment factors (Figure S2).

We performed sensitivity analyses for the final zBMI multiexposure model: *a*) We computed cohort-specific estimates and evaluated between-cohort heterogeneity of associations using the I^2 statistic as guidance (Higgins and Thompson 2002); *b*) The model was stratified by sex to obtain sex-specific estimates and sex interactions tested were tested by including an interaction term in the model, because of the sex-specificity of some environmental obesogens reported in the literature (Braun 2017); *c*) The model was stratified by maternal education (low to medium and high) to obtain education-specific estimates, and interactions were tested by including an interaction term in the model, to highlight any differences between socioeconomic classes; *d*) The models were additionally adjusted for social and lifestyle factors: The pregnancy exposure model was additionally adjusted for consumption of fast food, fruits, and vegetables during pregnancy (in tertiles) and moderate and vigorous physical activity during pregnancy (in minutes per day). The childhood exposure model was additionally adjusted for the FAS, for the KidMed, for child physical activity (moderate-to-vigorous, in minutes per day), and for child sleep duration (weighted average of weekday and weekend sleep hours per night). Diet, physical activity and sleep were not included in the main set of potential confounders (above), but only in these sensitivity analyses, because they may act as mediators for some exposures (e.g., physical activity may mediate an effect of green space on obesity); and *e*) Possible confounding by prenatal exposures in the childhood models was evaluated by including statistically significant exposure variables from the prenatal DSA model.

Results

Our study population included 1,301 mother–child pairs from the 6 cohorts (Table 2). Children were on average 8 years old at the examination (25th–75th percentile 6.5–8.9 y), with some variation by cohort (Table S5). The prevalence of overweight status and obesity combined was 28.8%, with 9.9% of children being obese (Table 2). The percentage of overweight and obese children was highest in the Spanish (42.6%) and Greek (37.2%) cohorts and lowest in the Norwegian cohort (15.8%) (Table S5). Maternal BMI and birth weight were strongly positively associated with child zBMI and overweight and obese status (Table S6).

Out of the 77 prenatal exposures studied, maternal smoking and maternal urinary cotinine concentration were the only two associated with a higher child zBMI in the ExWAS analysis at $p < 0.05$; these associations did not pass the multiple testing corrected p-value threshold of 0.001 (Figure 1; see Table S7 for ExWAS results). The DSA model identified maternal smoking as the only prenatal exposure contributing to zBMI (Table 3): Maternal active smoking was associated with an increase in the child's zBMI score of 0.28 [95% confidence interval (CI): 0.09,

Table 2. Description of the study population (total $N = 1,301$).

	N (%)	Percentiles: 25th; 50th; 75th	N missing
Cohort			
BiB, UK	205 (15.8)		0
EDEN, France	198 (15.2)		0
INMA, Spain	223 (17.1)		0
KANC, Lithuania	204 (15.9)		0
MoBa, Norway	272 (20.9)		0
Rhea, Greece	199 (15.3)		0
Age of the child at examination (y)		6.5; 8.1; 8.9	0
Sex of the child			0
Male	711 (54.7)		
Female	590 (45.3)		
Birthweight (g)		3,050; 3,380; 3,714	14
Maternal age at delivery (y)		27.2; 31.0; 34.0	16
Maternal prepregnancy BMI, kg/m^2		21.3; 23.9; 27.2	24
Maternal education level			44
Low (primary school)	173 (13.8)		
Middle (secondary school)	433 (34.5)		
High (university degree or higher)	651 (51.8)		
Parental country of origin			30
Both parents native	1,068 (84.0)		
None or one native parents	203 (16.0)		
Parity			31
Nulliparous	583 (45.9)		
Primiparous	460 (36.2)		
Multiparous	227 (17.9)		
Breastfeeding duration (wk)			353
<10.8	313 (33.0)		
10.8–34.9	314 (33.1)		
>34.9	321 (33.9)		
Child overweight/obese status			0
Normal or underweight	937 (71.3)		
Overweight and obese	374 (28.8)		
Obese	129 (9.9)		
BMI z-score		−0.39; 0.28; 1.10	0
Waist circumference z-score		−0.69; −0.25; 0.48	4
Skinfolds z-score		−0.68; −0.32; 0.34	13
Fat mass percentage z-score		−0.75; −0.15; 0.65	11

Note: BiB, Born in Bradford study cohort; BMI, body mass index; EDEN, Etude de cohorte généraliste, menée en France sur les Déterminants pré et post natals précoces du développement psychomoteur et de la santé de l'Enfant study cohort; INMA, INfancia y Medio Ambiente study cohort; KANC, Kaunas study cohort; MoBa, Norwegian Mother and Child Cohort; Rhea, Rhea Study Mother and Child Cohort.
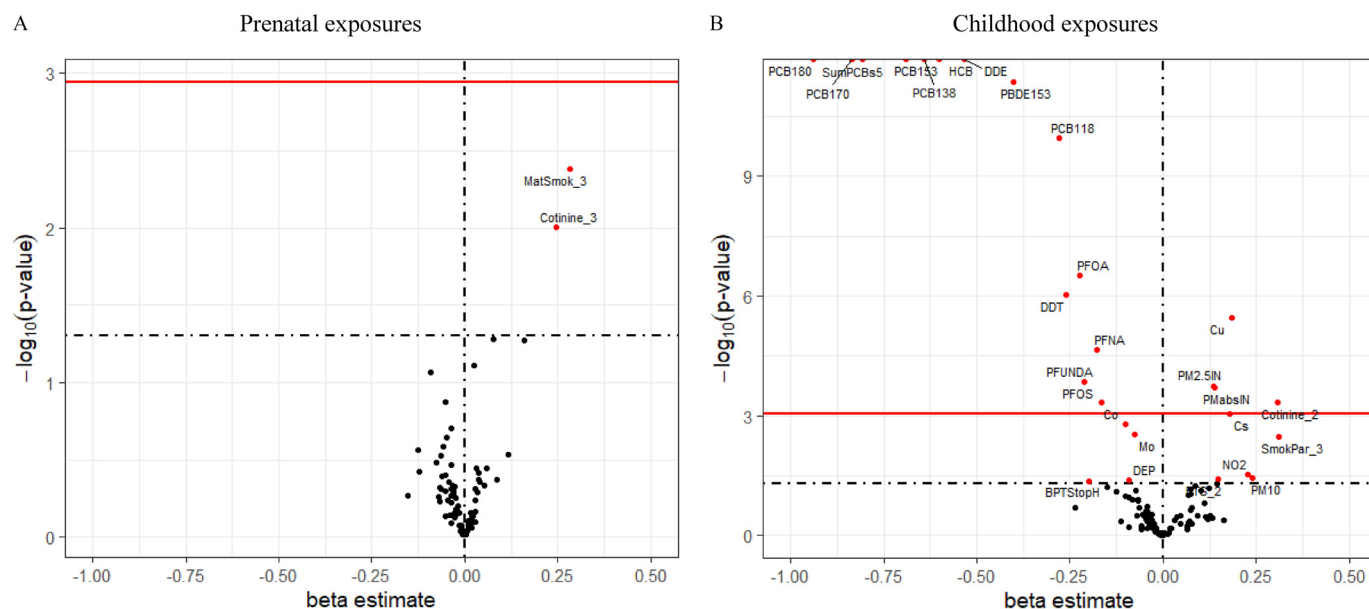
Figure 1. Association between prenatal and childhood exposures and zBMI in single-exposure ExWAS model. Volcano plot showing significance (*p*-value) against beta coefficient. [(A) Prenatal exposome and (B) childhood exposome]. Black dashed horizontal line at *p*-values of 0.05; red solid horizontal line at TEF of 0.001 (prenatal) and 0.0009 (childhood). Beta estimates for all exposures are shown in Table S17. Note: Beta coefficient for change in zBMI compared with reference category for the categorical variables. For continuous variables, beta estimates are calculated per interquartile range increase in exposure. TEF, threshold for effective number of test (i.e., *p*-value correction for multiple testing).

0.48], and maternal secondhand smoking with an increase of 0.16 (95% CI: −0.002, 0.32), in comparison with nonsmoking. Identification of active and secondhand smoking through maternal urinary cotinine levels gave similar associations (zBMI increase of 0.25 and 0.09, respectively) (Table S7). Maternal cotinine levels for active smoking and facility density were

borderline associated with an increased and decreased overweight and obesity risk, respectively ($p = 0.05$; Figure 2), but not selected by the DSA model.

In the childhood exposome, out of the 96 environmental exposures, 27 exposure variables showed associations with zBMI in the ExWAS at the $p < 0.05$ level, and 18 exposures remained

Table 3. Association between prenatal exposures (assessed during pregnancy) and childhood exposures (assessed at age 6–11 y) and zBMI or overweight and obesity in DSA multiexposure models ($N = 1,301$).

Exposure variable (IQR or reference category[a])	Exposure group	zBMI Beta for zBMI change[a] (95% CI)	Overweight and obesity status OR[a] (95% CI)
Prenatal exposures[b]			
Smoking in pregnancy	Tobacco smoking		
Secondhand smoking (vs. none)		0.16 (−0.02, 0.32)	
Active smoking (vs. none)		0.28 (0.09 to 0.48)	
Childhood exposures[c]			
Facility density (school) (38.9/km^2)	Built environment	−0.21 (−0.33, −0.08)	0.57 (0.40, 0.81)
Population density (home) (6,160/km^2)	Built environment	0.16 (0.07 to 0.25)	1.34 (1.04, 1.72)
Outdoor PM$_{2.5abs}$ (0.41 10^{-5}m^{-1})	Outdoor air pollution		1.31 (0.97, 1.76)
Road traffic load (11,38,814 vehicles/day)	Traffic		1.39 (1.02, 1.89)
Indoor PM$_{2.5abs}$ (0.50 10^{-5}m^{-1})	Indoor air pollution	0.08 (0.01, 0.15)	
Indoor NO$_2$ (92.8 µg/m^3)	Indoor air pollution	0.15 (0.01, 0.28)	
Cotinine detected (vs. not)	Tobacco smoking	0.20 (0.04, 0.37)	1.93 (1.28, 2.90)
DDE (34.0 ng/g lipids)	OCs	−0.20 (−0.30, −0.09)	
HCB (5.1 ng/g lipids)	OCs	−0.35 (−0.46, −0.25)	0.36 (0.25, 0.51)
Sum of PCBs (27.6 ng/g lipids)	OCs	−0.30 (−0.46, −0.15)	0.36 (0.22, 0.60)
PBDE153 (0.39 ng/g lipids)	PBDEs	−0.23 (−0.34, −0.13)	0.63 (0.47, 0.85)
Copper (186 µg/L)	Metals and elements	0.14 (0.07, 0.21)	1.37 (1.13, 1.66)
Cesium (0.73 µg/L)	Metals and elements	0.15 (0.06, 0.25)	1.57 (1.21, 2.04)
Cobalt (0.09 µg/L)	Metals and elements	−0.08 (−0.13, −0.02)	0.75 (0.63, 0.90)
Molybdenum (0.43 µg/L)	Metals and elements	−0.08 (−0.13, −0.04)	
DEP (4.04 µg/g)	OP Pesticides		0.74 (0.59, 0.92)
Social participation	Social/economic capital		
1 organization (vs. none)			0.82 (0.57, 1.18)
>1 organizations (vs. none)			1.74 (1.10, 2.74)

[a]Reference category as indicated inside brackets for the categorical variables. For continuous variables, estimates are calculated per interquartile range (IQR) increase in exposure, as indicated inside brackets; IQRs calculated on the first imputed dataset after back transforming the variables. BMI, body mass index; CI, confidence interval; DDE, 4,4′dichlorodiphenyldichloroethylene; DEP, diethyl phosphate; OCs, organochlorine compounds; HCB, hexachlorobenzene; OP, organophosphate; PBDEs, polybrominated diphenyl ethers; PBDE153, 2,2′,4,4′,5,5′-Hexabromodiphenyl ether; PCBs, polychlorinated biphenyls; zBMI, BMI z-scores.
[b]Adjusted for cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, and parental country of origin.
[c]Adjusted for cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding, and birth weight.
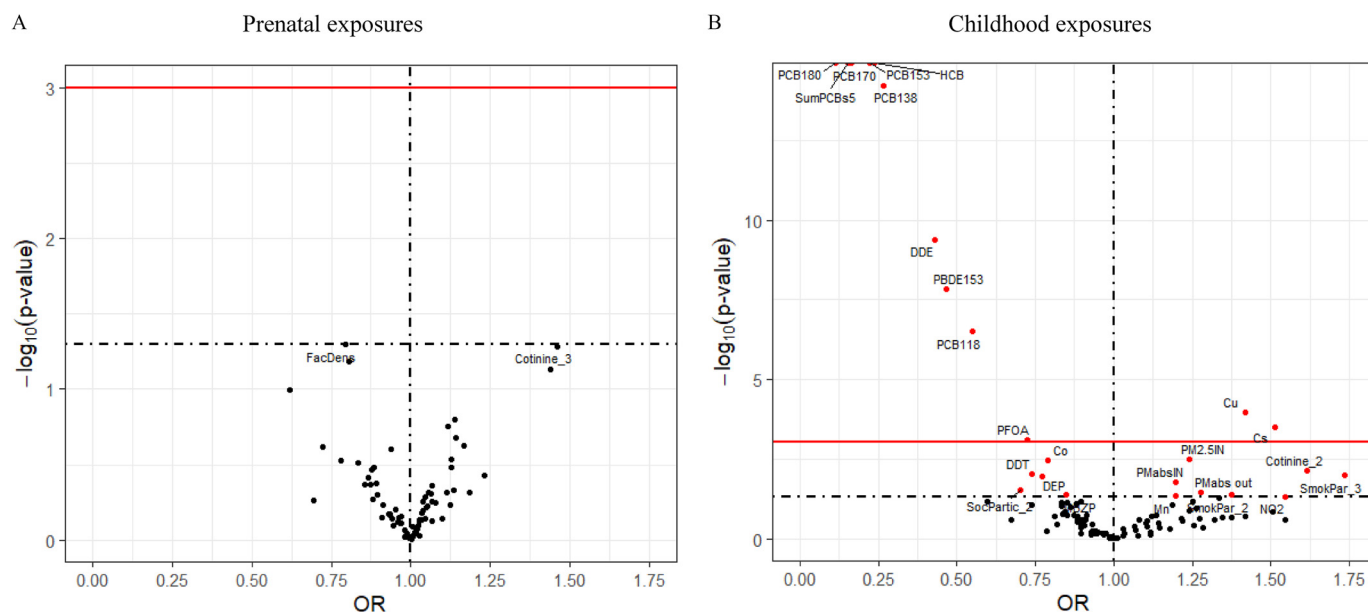
Figure 2. Association between prenatal and childhood exposures and overweight and obesity status in single-exposure exposure-wide association study (ExWAS) model. Volcano plot showing significance (*p*-value) against odds ratio (OR). [(A) prenatal exposome and (B) childhood exposome]. Black dashed horizontal line at *p*-values of 0.05; red solid horizontal line at TEF of 0.001 (prenatal) and 0.0009 (childhood). Note: OR, Odds-ratio for being overweight or obese in comparison with normal weight. OR for overweight and obesity status in comparison with reference category for the categorical variables. For continuous variables, ORs are calculated per interquartile range increase in exposure. TEF, threshold for effective number of test (i.e., *p*-value correction for multiple testing).

statistically significant when correcting for multiple testing (Figure 1; Table S7). The final multiexposure DSA model selected 13 variables (Table 3): population density near the home; absorbance of indoor $PM_{2.5abs}$; indoor NO_2 concentrations; and cotinine, copper, and cesium concentrations were associated with increased zBMI; in contrast, density of facilities near the school, and 4,4′dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), sum of PCBs, PBDE153, cobalt, and molybdenum concentrations were associated with reduced zBMI in children.

Results for overweight and obesity status were similar (Table 3; Figure 2; Table S8), but the final model notably included outdoor PM_{10} absorbance and road traffic load instead of indoor air pollutants, as well as social participation, which were each positively associated with overweight and obesity status, and diethyl phosphate (an OP pesticide metabolite) which was negatively associated with overweight and obesity status (Table 3). Findings for waist circumference, skinfolds, and fat mass closely mirrored the zBMI and overweight and obesity status results, with some small differences in the ranking of statistical significance and in the composition of the final multiexposure models (Tables S9–S11, and Figures S3–S5).

The observed associations were mostly consistent between cohorts and between sexes. No strong between-cohort heterogeneity (i.e., $I^2 > 25$) was observed in the zBMI multiexposure models for prenatal or childhood exposure, with the exception of HCB ($I^2 = 81$), sumPCBs ($I^2 = 43$), and molybdenum ($I^2 = 38$) (Figure S6). We observed little evidence for sex interactions (similar risk estimates and *p* value for interaction >0.1; Table S12). When results were stratified by maternal education (Table S13), the estimate for childhood cotinine level was stronger positive, and the estimates for DDE and HCB stronger negative in the low- or medium-education category; the estimates for indoor NO_2 and for copper were stronger positive in the higher education class (each with *p* value for interaction <0.2). When we added additional potential confounding variables to the models for prenatal exposure (maternal fast-food, fruits, and vegetables consumption, maternal physical activity) and childhood exposure (family affluence score, KidMed

score, child physical activity, and child sleep duration) in sensitivity analyses, effect estimates did not change by more than a few hundredths (Tables S14 and S15). When we added the prenatal maternal smoking to the main childhood multiexposure model, effect estimates did not change (Table S16).

Discussion

This study is, to our knowledge, the first systematic analysis of associations between many environmental exposures and childhood obesity. Our findings suggest that exposure to maternal smoking during pregnancy, childhood exposure to indoor and outdoor air pollutants, childhood passive smoke exposure, childhood residence in more densely populated areas, and attendance at school in areas with fewer facilities were associated with an increase in child BMI. Child blood levels of copper and cesium were associated with higher BMI; and levels of organochlorine pollutants, cobalt, and molybdenum were associated with lower BMI. Similar results were found for the other adiposity outcomes.

Maternal active smoking during pregnancy is a well-documented chemical obesogen associated with childhood obesity (Oken et al. 2008). Our findings are also in line with the majority of animal studies, which have shown that prenatal nicotine exposure is related to larger offspring fat mass and weight gains (Behl et al. 2013). Additionally, we observed an association with childhood exposure to SHS exposure. Previous studies also pointed toward this association (McConnell et al. 2015; Raum et al. 2011; Robinson et al. 2016) but found it difficult to disentangle effects of child SHS from correlated maternal smoking during pregnancy. In our study, adjustment of the childhood associations for maternal pregnancy smoking did not change results. We note also that the association between child cotinine levels and BMI was observed exclusively in the low and medium maternal education categories, where detectable child cotinine levels were far more prevalent (30% vs. 6% in high maternal education category). Preventive action to reduce SHS exposure of children should be aimed particularly at such families.

Regarding air pollution, a few previous studies suggested an association among traffic density, roadway proximity, or ambient air pollutant concentrations and childhood obesity (Jerrett et al. 2014; Kim et al. 2018; Lichtveld et al. 2018; McConnell et al. 2015). A few studies in animals also suggest that air pollutants such as PM_{10} can alter metabolism and increase weight gain (Bolton et al. 2012; Xu et al. 2010). In our study, home indoor air pollution exposure to PM_{10} absorbance (a marker of black or elemental carbon originating from combustion) and NO_2 were associated with increased BMI, whereas outdoor PM_{10} absorbance exposure was associated with increased overweight status and obesity risk. These findings were adjusted for correlated exposures such as SHS exposure. The association between indoor NO_2 and BMI was stronger in higher education categories, indicating that this association is not a lower social class result. We note that our estimates of indoor air pollution relied on prediction models using indoor measurements in 7%–12% of our study population, which may have introduced uncertainty in these estimates. However, the prediction models for indoor NO_2 and $PM_{2.5abs}$ had a reasonable explanatory value (*R*-squared 57% and 50%), similar to those reported for other indoor air pollution prediction models (Tong et al. 2019). Children spend much of their day at home indoors, and our study is the first to highlight the importance of assessing indoor air pollution when studying environmental obesogens.

The built environment may be an important driver of obesogenic behaviors, lifestyles, and exposures. We found that children living in densely population areas had higher BMI and body fat mass. Previous studies in children have reported both positive and negative associations (Schwartz et al. 2011; Yang et al. 2018), and results may be related to other constructs of the built environment, such as the food environment or area social deprivation (Schwartz et al. 2011), which we did not measure. The density of facilities around the school was associated with a reduction in BMI. Our facility density variable counted the number of facilities, such as businesses, community services, educational institutions, restaurants, and shops in an area. Facility density is an indicator of how walkable an area may be and indeed was highly correlated with the walkability index in our data (correlation coefficient 0.72), so this finding is in line with other studies on walkability effects (Gascon et al. 2016; Lichtveld et al. 2018). We should also note that our findings for childhood exposures are based on cross-sectional data, which require follow-up in prospective settings to examine longer term impacts.

Experimental studies indicate that certain chemical contaminants may act as obesogens, but epidemiological evidence remains inconclusive (Braun 2017; Thayer et al. 2012). In our study, the largest to date for several compounds (e.g., parabens, triclosan), we did not observe associations with increased obesity outcomes for most of the chemical groups under study. Null associations observed for the highly variable nonpersistent chemicals (phthalates, phenols, OP pesticides) may be explained by attenuation bias related to the high levels of measurement error in spot urine measurements (Casas et al. 2018), even though our pooling of two urine samples in the childhood biomarker analysis would have alleviated this bias somewhat. Attenuation bias would particularly apply to our results for bisphenol A, some phthalate metabolites, such as DEHP metabolites, and OP pesticide metabolites; for these compounds, the attenuation bias for a single spot urine measurement may be as high as 70%–90% (Perrier et al. 2016; Rappaport et al. 1995).

We observed associations of reduced BMI with increased childhood serum concentrations of most persistent organic pollutants, especially DDE, HCB, PCBs, and PBDE153. In the literature, cross-sectional associations between persistent organic pollutant (POP) levels in serum and BMI in adults and children have been highly inconsistent, showing negative, positive, or no associations (Iszatt et al. 2015; Jackson et al. 2017; Rönn et al. 2011; Windham et al. 2010; Wood et al. 2016). POPs are highly lipophilic (they store in fat tissue), and the amount of body fat in an individual is expected to affect the toxicokinetics of POPs (Jackson et al. 2017; Wood et al. 2016). It has been reported that the equilibrium between the storage of POPs in fat tissue and their circulation in blood would be disturbed in particular during times of increasing or decreasing exposure and during weight gain or weight loss (Jackson et al. 2017). Studies have shown, for example, that weight loss leads to increasing circulating POP serum levels (Dirinck et al. 2015; Malarvannan et al. 2018). It is not clear how complex toxicokinetics would influence the POPs–BMI associations in growing children by obesity status, but this is expected to depend on growth rates, amount of fat tissue, type of fat tissue (visceral or subcutaneous), age, and exposure dose and timing (Jackson et al. 2017; Wolff et al. 2007; Wood et al. 2016). The possibility of nonmonotonic (e.g., inverted U-shaped) dose–response relationships for endocrine-disrupting chemicals has also been proposed as an explanation for the findings of greater health effects at lower doses of exposure (Jackson et al. 2017; Schug et al. 2016). We examined the shape of the dose–response relationships for all our exposures and did not find evidence of nonmonotonic shapes (not shown); in fact, dose–response curves declined linearly for the all childhood POP exposures. Our results highlight the need for longitudinal follow-up of these findings, as well as for a better understanding of POPs toxicokinetics during childhood growth years in general.

We observed consistent associations between concentrations of metallic elements measured in blood and obesity outcomes, with positive associations (higher BMI with higher blood concentration) for copper and cesium, and negative associations (lower BMI with higher blood concentration) for cobalt and molybdenum. With the exception of cesium, these are essential trace elements in humans that play a role in the synthesis and activation of many enzymes and in the regulation of glucose and lipid metabolism (Li and Yang 2018; Morrell et al. 2017). At the same time, the toxicity of each has been documented at high (occupational level) exposure levels. Other cross-sectional studies based on the large NHANES child population (6–19 y) have pointed toward strongly positive associations between copper and manganese and obesity status (Fan et al. 2017) and negative associations for cobalt (Shao et al. 2017), similar to associations in our results. Raised copper levels in obese children have also been documented in other cross-sectional studies (Azab et al. 2014; Lima et al. 2006) and in adult obesity patients (Yang et al. 2019). These associations may indicate a role of these elements in fat accumulation, or they may indicate that physiological changes in overweight and obese children result in altered blood levels of these elements, but there is currently little information on the mechanisms behind any relationship between elements such as copper and obesity (Yang et al. 2019; Li and Yang 2018). Our cross-sectional results observed for the metals and elements are novel and require further follow-up in longitudinal studies.

The main strengths of our study are first, the comprehensive assessment of environmental exposures in two critical developmental time periods (pregnancy and childhood) and inclusion of highly sensitive biomarkers for many chemical exposures and wide-ranging geospatial modeling of the outdoor and built environment. We note that most of the associations we observed were related to childhood exposures, whereas very few associations were apparent for pregnancy exposures. It is unclear from the literature when the strongest associations would be expected, and different exposures may act during different developmental periods, making it important to cover multiple periods (Lichtveld et al. 2018). Second, our study included a relatively large sample size for

which we were able to measure many exposures. Others have demonstrated that an ExWAS approach combined with FDR multiple testing correction would require sample size of z-2000 subjects to deal with 100 exposures and achieve a power of 80% in the setting of a study on male fertility–related outcomes (Chung et al. 2019). Third, our study included a comprehensive assessment of obesity and adiposity outcomes, which allowed evaluation of the consistency of associations between BMI as a fairly crude obesity measure and more specific measures of abdominal, subcutaneous, and total body fat mass. Indeed, these different outcomes showed very similar results. Future studies may consider the inclusion of better estimation of body fat mass distribution, such as magnetic resonance imaging. Fourth, our study included the use of an optimal combination of *a priori* selected statistical approaches based on results of simulation studies (Agier et al. 2016; Barrera-Gómez et al. 2017). We used the ExWAS screening method that is characterized by its low false-negative rate and high sensitivity and the DSA that has a low false-positive rate and allowed adjustment for confounding by multiple exposures.

We also acknowledge several limitations. First, the part of our study that focused on childhood exposures was cross-sectional in nature. This aspect particularly limited our interpretation of results for chemical contaminants because they may suffer from reverse causation bias, whereby obesity status would influence a biomarker's toxicokinetics and thus its circulating concentration, instead of vice versa. For other cross-sectionally assessed exposures found to be associated with child BMI in our study (childhood exposure to indoor and outdoor air pollutants, childhood passive smoke exposure, childhood residence in more densely populated areas, and facility density near school), reverse causality bias is of less of concern, because it is unlikely that the obesity status of the child influenced these exposures. Still, a clear temporal sequence between exposure and health outcome would strengthen any causal interpretation of associations.

Second, the different exposures are measured with different types and levels of measurement error. For example, as explained above, urine levels of nonpersistent chemicals have a high intra-individual variability (Casas et al. 2018) and are expected to suffer particularly from classical-type measurement error. Exposures measured by models and questionnaires are expected to suffer from other types of measurement errors; for example, modeled outdoor air pollutants estimated at the residential address are not well correlated with short-term personal air pollution levels (Nieuwenhuijsen et al. 2015). Although some estimates of classical-type error are available from intraclass correlation coefficients published in the literature (Casas et al. 2018; Perrier et al. 2016), this information was not available for the majority of our exposure variables, and we did therefore not attempt to correct for measurement errors. As a result, we cannot directly compare the effect size and significance levels between exposures, and we advise against using our results to rank the importance of exposure in terms of their influence on obesity risk.

Third, we focused on many environmental chemical and non-chemical exposures that are suspected to play a role in the development of childhood obesity (Lichtveld et al. 2018), but we could not include all factors and do not cover a complete exposome.

Fourth, we cannot exclude unmeasured residual confounding, in particular with respect to unmeasured social factors related to childhood obesity. We note though that most results were robust to stratification by maternal education and to adjustment by family affluence score, diet quality, sleep, and physical activity. Residual confounding by further social or lifestyle factors would therefore be expected to have minimal effects.

Last, we recognize that the small HELIX subcohort (N around 200 in each country) may not be representative of the general population in each country; overweight status and obesity prevalence rates in some of our cohorts were similar to those reported for their country by the large comprehensive NCD-RisC study [NCD Risk Factor Collaboration (NCD-RisC) 2017] in the 5–19 y age group (Rhea and EDEN cohorts), but lower than the NCD-RisC prevalence found in BiB and MoBa, and higher in INMA and KANC cohorts.

The exposome approach we adopted aimed at systematically publishing all exposure–outcome associations, independently of their magnitude or statistical significance, thus avoiding publication bias. Further, this approach corrected for multiple testing to reduce false-positive results, which is not done when studies publish results in a series of papers with each focusing on a single exposure or exposure group. Last, confounding by other exposures is usually not tackled in single-exposure studies. Exposome studies, by including many exposure variables, can account for this. Indeed, we were able to include many components of the exposome in relatively large populations, rather than studying its components in isolation. Ultimately, once challenges such as multiple exposure measurement errors, reverse causality, and confounding have been sufficiently tackled, the exposome approach may have value both in discovery of new risk factors and in the setting of priorities for prevention. We specifically note that any increase the number of exposures considered in future exposome studies should not be done at the cost of a decrease in the accuracy of estimation of each exposure.

In conclusion, this first systematic analysis of many suspected environmental obesogens during critical early-life periods, strengthens evidence of the contribution of exposure to tobacco smoke and air pollution and characteristics of the built environment to the development of childhood obesity. These results may help to identify targets for prevention and intervention early in life, leading to better science-based regulation of environmental obesogenic exposures.

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The HELIX data warehouse has been established as an accessible resource for collaborative research involving researchers external to the project. Access to HELIX data is based on approval by the HELIX Project Executive Committee and by the individual cohorts. Further details on the content of the data warehouse (data catalog) and procedures for external access are described on the project website (http://www.projecthelix.eu/index.php/es/data-inventory).

References

Agay-Shay K, Martinez D, Valvi D, Garcia-Esteban R, Basagaña X, Robinson O, et al. 2015. Exposure to endocrine-disrupting chemicals during pregnancy and weight at 7 years of age: a multi-pollutant approach. Environ Health Perspect 123(10):1030–1037, PMID: 25956007, https://doi.org/10.1289/ehp.1409049.

Agier L, Basagaña X, Maitre L, Granum B, Bird PK, Casas M, et al. 2019. Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. Lancet Planet Health 3(2):e81–e92, PMID: 30737192, https://doi.org/10.1016/S2542-5196(19)30010-5.

Agier L, Portengen L, Chadeau-Hyam M, Basagaña X, Giorgis-Allemand L, Siroux V, et al. 2016. A systematic comparison of linear regression–based statistical methods to assess exposome-health associations. Environ Health Perspect 124(12):1848–1856, PMID: 27219331, https://doi.org/10.1289/EHP172.

Aurrekoetxea JJ, Murcia M, Rebagliato M, López MJ, Castilla AM, Santa-Marina L, et al. 2013. Determinants of self-reported smoking and misclassification during pregnancy, and analysis of optimal cut-off points for urinary cotinine: a cross-sectional study. BMJ Open 3(1):e002034, PMID: 23355667, https://doi.org/10.1136/bmjopen-2012-002034.

Azab SFA, Saleh SH, Elsaeed WF, Elshafie MA, Sherief LM, Esh A. 2014. Serum trace elements in obese Egyptian children: a case-control study. Ital J Pediatr 40(1):20, PMID: 24555483, https://doi.org/10.1186/1824-7288-40-20.

Barrera-Gómez J, Agier L, Portengen L, Chadeau-Hyam M, Giorgis-Allemand L, Siroux V, et al. 2017. A systematic comparison of statistical methods to detect interactions in exposome-health associations. Environ Health 16(1):74, PMID: 28709428, https://doi.org/10.1186/s12940-017-0277-6.

Beelen R, Hoek G, Pebesma E, Vienneau D, de Hoogh K, Briggs DJ. 2009. Mapping of background air pollution at a fine spatial scale across the European Union. Sci Total Environ 407(6):1852–1867, https://doi.org/10.1016/j.scitotenv.2008.11.048.

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO$_2$ and NO$_x$ land use regression models for estimating air pollution exposure in 36 study areas in Europe–the ESCAPE project. Atmos Environ 72:10–23, https://doi.org/10.1016/j.atmosenv.2013.02.037.

Behl M, Rao D, Aagaard K, Davidson TL, Levin ED, Slotkin TA, et al. 2013. Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a National Toxicology Program workshop review. Environ Health Perspect 121(2):170–180, PMID: 23232494, https://doi.org/10.1289/ehp.1205404.

Bolton JL, Smith SH, Huff NC, Gilmour MI, Foster WM, Auten RL, et al. 2012. Prenatal air pollution exposure induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner. FASEB J 26(11):4743–4754, PMID: 22815382, https://doi.org/10.1096/fj.12-210989.

Boyce W, Torsheim T, Currie C, Zambon A. 2006. The family affluence scale as a measure of national wealth: validation of an adolescent self-report measure. Soc Indic Res 78(3):473–487, https://doi.org/10.1007/s11205-005-1607-6.

Braun JM. 2017. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat Rev Endocrinol 13(3):161–173, PMID: 27857130, https://doi.org/10.1038/nrendo.2016.186.

Casas M, Basagaña X, Sakhi AK, Haug LS, Philippat C, Granum B, et al. 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ Int 121:561–573, PMID: 30300814, https://doi.org/10.1016/j.envint.2018.09.046.

Chatzi L, Leventakou V, Vafeiadi M, Koutra K, Roumeliotaki T, Chalkiadaki G, et al. 2017. Cohort profile: the Mother-Child Cohort in Crete, Greece (Rhea Study). Int J Epidemiol 46(5):1392–1393k, PMID: 29040580, https://doi.org/10.1093/ije/dyx084.

Chung MK, Buck Louis GM, Kannan K, Patel CJ. 2019. Exposome-wide association study of semen quality: systematic discovery of endocrine disrupting chemical biomarkers in fertility require large sample sizes. Environ Int 125:505–514, PMID: 30583854, https://doi.org/10.1016/j.envint.2018.11.037.

Clasey JL, Bradley KD, Bradley JW, Long DE, Griffith JR. 2011. A new BIA equation estimating the body composition of young children. Obesity (Silver Spring) 19(9):1813–1817, PMID: 21681223, https://doi.org/10.1038/oby.2011.158.

Cyrys J, Eeftens M, Heinrich J, Ampe C, Armengaud A, Beelen R, et al. 2012. Variation of NO$_2$ and NO$_x$ concentrations between and within 36 European study areas: results from the ESCAPE study. Atmos Environ 62:374–390, https://doi.org/10.1016/j.atmosenv.2012.07.080.

de Onis M, Lobstein T. 2010. Defining obesity risk status in the general childhood population: which cut-offs should we use? Int J Pediatr Obes 5(6):458–460, PMID: 20233144, https://doi.org/10.3109/17477161003615583.

de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. 2007. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 85(9):660–667, PMID: 18026621, https://doi.org/10.2471/blt.07.043497.

Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and management of environmental noise. 2002. Off J Eur Communities 45:12–26.

Dirinck E, Dirtu AC, Jorens PG, Malarvannan G, Covaci A, Van Gaal LF. 2015. Pivotal role for the visceral fat compartment in the release of persistent organic pollutants during weight loss. J Clin Endocrinol Metab 100(12):4463–4471, PMID: 26469381, https://doi.org/10.1210/jc.2015-2571.

Duncan DT, Aldstadt J, Whalen J, Melly SJ, Gortmaker SL. 2011. Validation of Walk Score® for estimating neighborhood walkability: an analysis of four US metropolitan areas. IJERPH 8(11):4160–4179, PMID: 22163200, https://doi.org/10.3390/ijerph8114160.

Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012a. Development of land use regression models for PM$_{2.5}$, PM$_{2.5}$ absorbance, PM$_{10}$ and PM$_{coarse}$ in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.

Eeftens M, Tsai M-Y, Ampe C, Anwander B, Beelen R, Bellander T, et al. 2012b. Spatial variation of PM$_{2.5}$, PM$_{10}$, PM$_{2.5}$ absorbance and PM$_{coarse}$ concentrations between and within 20 European study areas and the relationship with NO$_2$– Results of the ESCAPE project. Atmos Environ 62:303–317, https://doi.org/10.1016/j.atmosenv.2012.08.038.

European Environmental Agency. 2010. Urban Atlas. [dataset]. https://www.eea.europa.eu/data-and-maps/data/urban-atlas [accessed 28 May 2014].

Fan Y, Zhang C, Bu J. 2017. Relationship between selected serum metallic elements and obesity in children and adolescent in the U.S. Nutrients 9(2):104, PMID: 28165362, https://doi.org/10.3390/nu9020104.

Frank LD, Sallis JF, Conway TL, Chapman JE, Saelens BE, Bachman W. 2006. Many pathways from land use to health: associations between neighborhood walkability and active transportation, body mass index, and air quality. J Am Plan Assoc 72(1):75–87, https://doi.org/10.1080/01944360608976725.

Gascon M, Vrijheid M, Nieuwenhuijsen MJ. 2016. The built environment and child health: an overview of current evidence. Curr Environ Health Rep 3(3):250–257, PMID: 27220615, https://doi.org/10.1007/s40572-016-0094-z.

Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. 2018. Acceleration of BMI in early childhood and risk of sustained obesity. N Engl J Med 379(14):1303–1312, PMID: 30281992, https://doi.org/10.1056/NEJMoa1803527.

Giorgis-Allemand L, Pedersen M, Bernard C, Aguilera I, Beelen RMJ, Chatzi L, et al. 2017. The influence of meteorological factors and atmospheric pollutants on the risk of preterm birth. Am J Epidemiol 185(4):247–258, PMID: 28087514, https://doi.org/10.1093/aje/kww141.

Goñi F, López R, Etxeandia A, Millán E, Amiano P. 2007. High throughput method for the determination of organochlorine pesticides and polychlorinated biphenyls in human serum. J Chromatogr B Anal Technol Biomed Life Sci 852(1–2):15–21, PMID: 17267299, https://doi.org/10.1016/j.jchromb.2006.12.049.

Gorman S, Lucas RM, Allen-Hall A, Fleury N, Feelisch M. 2017. Ultraviolet radiation, vitamin D and the development of obesity, metabolic syndrome and type-2 diabetes. Photochem Photobiol Sci 16(3):362–373, PMID: 28009891, https://doi.org/10.1039/c6pp00274a.

Grazuleviciene R, Danileviciute A, Nadisauskiene R, Vencloviene J. 2009. Maternal smoking, GSTM1 and GSTT1 polymorphism and susceptibility to adverse pregnancy outcomes. IJERPH 6(3):1282–1297, PMID: 19440446, https://doi.org/10.3390/ijerph6031282.

Grimvall E, Rylander L, Nilsson-Ehle P, Nilsson U, Strömberg U, Hagmar L, et al. 1997. Monitoring of polychlorinated biphenyls in human blood plasma: methodological developments and influence of age, lactation, and fish consumption. Arch Environ Contam Toxicol 32(3):329–336, PMID: 9096084, https://doi.org/10.1007/s002449900193.

Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J, et al. INMA Project. 2012. Cohort profile: the INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. Int J Epidemiol 41(4):930–940, PMID: 21471022, https://doi.org/10.1093/ije/dyr054.

Haug LS, Sakhi AK, Cequier E, Casas M, Maitre L, Basagaña X, et al. 2018. In-utero and childhood chemical exposome in six European mother-child cohorts. Environ Int 121:751–763, PMID: 30326459, https://doi.org/10.1016/j.envint.2018.09.056.

Heude B, Forhan A, Slama R, Douhaud L, Bedel S, Saurel-Cubizolles M-J, et al. 2016. EDEN mother-child cohort study group. 2016. Cohort profile: the EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. Int J Epidemiol 45(2):353–363, PMID: 26283636, https://doi.org/10.1093/ije/dyv151.

Higgins JPT, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558, PMID: 12111919, https://doi.org/10.1002/sim.1186.

Iszatt N, Stigum H, Verner MA, White RA, Govarts E, Murinova LP, et al. OBELIX. 2015. Prenatal and postnatal exposure to persistent organic pollutants and infant growth: a pooled analysis of seven European birth cohorts. Environ Health Perspect 123(7):730–736, PMID: 25742056, https://doi.org/10.1289/ehp.1308005.

Jackson E, Shoemaker R, Larian N, Cassis L. 2017. Adipose tissue as a site of toxin accumulation. Compr Physiol 7(4):1085–1135, PMID: 28915320, https://doi.org/10.1002/cphy.c160038.

Janesick AS, Blumberg B. 2016. Obesogens: an emerging threat to public health. Am J Obstet Gynecol 214(5):559–565, PMID: 26829510, https://doi.org/10.1016/j.ajog.2016.01.182.

Jeong CH, Wagner ED, Siebert VR, Anduri S, Richardson SD, Daiber EJ, et al. 2012. Occurrence and toxicity of disinfection byproducts in European drinking waters in relation with the HIWATE Epidemiology Study. Environ Sci Technol 46(21):12120–12128, PMID: 22958121, https://doi.org/10.1021/es3024226.

Jerrett M, McConnell R, Wolch J, Chang R, Lam C, Dunton G, et al. 2014. Traffic-related air pollution and obesity formation in children: a longitudinal, multilevel analysis. Environ Health 13:49, PMID: 24913018, https://doi.org/10.1186/1476-069X-13-49.

Jin Y, Hein MJ, Deddens JA, Hines CJ. 2011. Analysis of lognormally distributed exposure data with repeated measures and values below the limit of detection using SAS. Ann Occup Hyg 55(1):97–112, PMID: 21177260, https://doi.org/10.1093/annhyg/meq061.

Kim JS, Alderete TL, Chen Z, Lurmann F, Rappaport E, Habre R, et al. 2018. Longitudinal associations of in utero and early life near-roadway air pollution with trajectories of childhood body mass index. Environ Health 17(1):64, PMID: 30213262, https://doi.org/10.1186/s12940-018-0409-7.

Koponen J, Rantakokko P, Airaksinen R, Kiviranta H. 2013. Determination of selected perfluorinated alkyl acids and persistent organic pollutants from a small volume human serum sample relevant for epidemiological studies. J Chromatogr A 1309:48–55, PMID: 23972455, https://doi.org/10.1016/j.chroma.2013.07.064.

Lachowycz K, Jones AP. 2011. Greenspace and obesity: a systematic review of the evidence. Obes Rev 12(5):e183–e9, PMID: 21348919, https://doi.org/10.1111/j.1467-789X.2010.00827.x.

Li L, Yang X. 2018. The essential element manganese, oxidative stress, and metabolic diseases: links and interactions. Oxid Med Cell Longev 2018:7580707, PMID: 29849912, https://doi.org/10.1155/2018/7580707.

Li M-X, Yeung JMY, Cherny SS, Sham PC. 2012. Evaluating the effective numbers of independent tests and significant p-value thresholds in commercial genotyping arrays and public imputation reference datasets. Hum Genet 131(5):747–756, PMID: 22143225, https://doi.org/10.1007/s00439-011-1118-2.

Lichtveld K, Thomas K, Tulve NS. 2018. Chemical and non-chemical stressors affecting childhood obesity: a systematic scoping review. J Expo Sci Environ Epidemiol 28(1):1–12, PMID: 28952603, https://doi.org/10.1038/jes.2017.18.

Lima S, Arrais RF, Sales CH, Almeida MG, de Sena KCM, Oliveira VTL, et al. 2006. Assessment of copper and lipid profile in obese children and adolescents. Biol Trace Elem Res 114 114(1–3):19–29, PMID: 17205984, https://doi.org/10.1385/BTER:114:1:19.

Liu Y, Wang M, Villberg J, Torsheim T, Tynjälä J, Lv Y, et al. 2012. Reliability and validity of Family Affluence Scale (FAS II) among adolescents in Beijing, China. Child Ind Res 5(2):235–251, https://doi.org/10.1007/s12187-011-9131-5.

Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, et al. 2016. Cohort profile update: the Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 45(2):382–388, PMID: 27063603, https://doi.org/10.1093/ije/dyw029.

Maitre L, de Bont J, Casas M, Robinson O, Aasvang GM, Agier L, et al. 2018. Human Early Life Exposome (HELIX) study: a European population-based exposome cohort. BMJ Open 8(9):e021311, PMID: 30206078, https://doi.org/10.1136/bmjopen-2017-021311.

Malarvannan G, Van Hoorenbeeck K, Deguchtenaere A, Verhulst SL, Dirinck E, Van Gaal L, et al. 2018. Dynamics of persistent organic pollutants in obese adolescents during weight loss. Environ Int 110:80–87, PMID: 29107350, https://doi.org/10.1016/j.envint.2017.10.009.

Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Basterrechea M, Grimalt JO, et al. 2015. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ Res 142:471–478, PMID: 26257032, https://doi.org/10.1016/j.envres.2015.07.020.

McAllister EJ, Dhurandhar NV, Keith SW, Aronne LJ, Barger J, Baskin M, et al. 2009. Ten putative contributors to the obesity epidemic. Crit Rev Food Sci Nutr 49(10):868–913, PMID: 19960394, https://doi.org/10.1080/10408390903372599.

McConnell R, Shen E, Gilliland FD, Jerrett M, Wolch J, Chang C-C, et al. 2015. A longitudinal cohort study of body mass index and childhood exposure to secondhand tobacco smoke and air pollution: the Southern California Children's Health Study. Environ Health Perspect 123(4):360–366, PMID: 25389275, https://doi.org/10.1289/ehp.1307031.

Morrell A, Tallino S, Yu L, Burkhead JL. 2017. The role of insufficient copper in lipid synthesis and fatty-liver disease. IUBMB Life 69(4):263–270, PMID: 28271632, https://doi.org/10.1002/iub.1613.

NCD Risk Factor Collaboration (NCD-RisC). 2017. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 390:2627–2642, PMID: 29029897, https://doi.org/10.1016/S0140-6736(17)32129-3.

NHANES III Body Measurements (Anthropometry). 1988, https://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/NCHS/MANUALS/ANTHRO.PDF [accessed 10 June 2017].

Nieuwenhuijsen MJ, Agier L, Basagaña X, Urquiza J, Tamayo-Uria I, Giorgis-Allemand L, et al. 2019. Influence of the urban exposome on birth weight. Environ Health Perspect 127(4):47007, https://doi.org/10.1289/EHP3971.

Nieuwenhuijsen MJ, Donaire-Gonzalez D, Rivas I, de Castro M, Cirach M, Hoek G, et al. 2015. Variability in and agreement between modeled and personal continuously measured black carbon levels using novel smartphone and sensor technologies. Environ Sci Technol 49(5):2977–2982, PMID: 25621420, https://doi.org/10.1021/es505362x.

Nieuwenhuijsen MJ, Kruize H, Gidlow C, Andrusaityte S, Antó JM, Basagaña X, et al. 2014. Positive health effects of the natural outdoor environment in typical populations in different regions in Europe (PHENOTYPE): a study programme protocol. BMJ Open 4(4):e004951, PMID: 24740979, https://doi.org/10.1136/bmjopen-2014-004951.

Oken E, Levitan EB, Gillman MW. 2008. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. Int J Obes (Lond) 32(2):201–210, PMID: 18278059, https://doi.org/10.1038/sj.ijo.0803760.

OpenStreetMap® Website. Available: https://www.openstreetmap.org/.

Park MH, Falconer C, Viner RM, Kinra S. 2012. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. Obes Rev 13(11):985–1000, PMID: 22731928, https://doi.org/10.1111/j.1467-789X.2012.01015.x.

Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen A-M, Ballester F, et al. 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med 1(9):695–704, PMID: 24429273, https://doi.org/10.1016/S2213-2600(13)70192-9.

Perrier F, Giorgis-Allemand L, Slama R, Philippat C. 2016. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. Epidemiology 27(3):378–388, PMID: 27035688, https://doi.org/10.1097/EDE.0000000000000460.

Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, et al. 2011. Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ Health Perspect, PMID: 21900077.

Poothong S, Thomsen C, Padilla-Sanchez JA, Papadopoulou E, Haug LS. 2017. Distribution of novel and well-known poly- and perfluoroalkyl substances (PFASs) in human serum, plasma, and whole blood. Environ Sci Technol 51(22):13388–13396, PMID: 29056041, https://doi.org/10.1021/acs.est.7b03299.

Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ögren M, et al. 2017. Long-term exposure to transportation noise in relation to development of obesity—a cohort study. Environ Health Perspect 125(11):117005, PMID: 29161230, https://doi.org/10.1289/EHP1910.

Quek Y-H, Tam WWS, Zhang MWB, Ho R. 2017. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. Obes Rev 18(7):742–754, PMID: 28401646, https://doi.org/10.1111/obr.12535.

Rahmalia A, Giorgis-Allemand L, Lepeule J, Philippat C, Galineau J, Hulin A, et al. 2012. Pregnancy exposure to atmospheric pollutants and placental weight: an approach relying on a dispersion model. Environ Int 48:47–55, PMID: 22836169, https://doi.org/10.1016/j.envint.2012.06.013.

Ramon R, Murcia M, Aguinagalde X, Amurrio A, Llop S, Ibarluzea J, et al. 2011. Prenatal mercury exposure in a multicenter cohort study in Spain. Environ Int 37(3):597–604, PMID: 21239061, https://doi.org/10.1016/j.envint.2010.12.004.

Rappaport SM, Symanski E, Yager JW, Kupper LL. 1995. The relationship between environmental monitoring and biological markers in exposure assessment. Environ Health Perspect 103:49–53, PMID: 7635112, https://doi.org/10.2307/3432560.

Raum E, Küpper-Nybelen J, Lamerz A, Hebebrand J, Herpertz-Dahlmann B, Brenner H. 2011. Tobacco smoke exposure before, during, and after pregnancy and risk of overweight at age 6. Obesity (Silver Spring) 19(12):2411–2417, PMID: 21617637, https://doi.org/10.1038/oby.2011.129.

Robinson O, Martínez D, Aurrekoetxea JJ, Estarlich M, Somoano AF, Íñiguez C, et al. 2016. The association between passive and active tobacco smoke exposure and child weight status among Spanish children. Obesity (Silver Spring) 24(8):1767–1777, PMID: 27367931, https://doi.org/10.1002/oby.21558.

Robinson O, Tamayo I, de Castro M, Valentin A, Giorgis-Allemand L, Hjertager Krog N, et al. 2018. The urban exposome during pregnancy and its socioeconomic determinants. Environ Health Perspect 126(7):077005, PMID: 30024382, https://doi.org/10.1289/EHP2862.

Rönn M, Lind L, van Bavel B, Salihovic S, Michaëlsson K, Lind PM. 2011. Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans. Chemosphere 85(3):335–343, PMID: 21767864, https://doi.org/10.1016/j.chemosphere.2011.06.095.

Saelens BE, Glanz K, Frank LD, Couch SC, Zhou C, Colburn T, et al. 2018. Two-year changes in child weight status, diet, and activity by neighborhood nutrition and physical activity environment. Obesity (Silver Spring) 26(8):1338–1346, PMID: 30138547, https://doi.org/10.1002/oby.22247.

Schembari A, de Hoogh K, Pedersen M, Dadvand P, Martinez D, Hoek G, et al. 2015. Ambient air pollution and newborn size and adiposity at birth: differences by maternal ethnicity (the Born in Bradford Study Cohort). Environ Health Perspect 123(11):1208–1215, PMID: 25978617, https://doi.org/10.1289/ehp.1408675.

Schug TT, Johnson AF, Birnbaum LS, Colborn T, Guillette LJ, Crews DP, et al. 2016. Minireview: endocrine disruptors: past lessons and future directions. Mol Endocrinol 30(8):833–847, PMID: 27477640, https://doi.org/10.1210/me.2016-1096.

Schwartz BS, Stewart WF, Godby S, Pollak J, DeWalle J, Larson S, et al. 2011. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med 41(4):e17–e28, PMID: 21961475, https://doi.org/10.1016/j.amepre.2011.06.038.

Serra-Majem L, Ribas L, Ngo J, Ortega RM, García A, Pérez-Rodrigo C, et al. 2004. Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. Public Health Nutr 7(7):931–935, PMID: 15482620, https://doi.org/10.1079/PHN2004556.

Shannon CE. 2001. A mathematical theory of communication. ACM SIGMOBILE Mob Comput Commun Rev 5(1):3–55, https://doi.org/10.1145/584091.584093.

Shao W, Liu Q, He X, Liu H, Gu A, Jiang Z. 2017. Association between level of urinary trace heavy metals and obesity among children aged 6-19 years: NHANES 1999–2011. Environ Sci Pollut Res Int 24(12):11573–11581, PMID: 28321702, https://doi.org/10.1007/s11356-017-8803-1.

Singh AS, Mulder C, Twisk JWR, van Mechelen W, Chinapaw M. 2008. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 9(5):474–488, PMID: 18331423, https://doi.org/10.1111/j.1467-789X.2008.00475.x.

Sinisi SE, van der Laan MJ. 2004. Deletion/substitution/addition algorithm in learning with applications in genomics. Stat Appl Genet Mol Biol 3:Article18, PMID: 16646796, https://doi.org/10.2202/1544-6115.1069.

Smargiassi A, Goldberg MS, Plante C, Fournier M, Baudouin Y, Kosatsky T. 2009. Variation of daily warm season mortality as a function of micro-urban heat islands. J Epidemiol Community Health 63(8):659–664, PMID: 19366997, https://doi.org/10.1136/jech.2008.078147.

Stern AH, Smith AE. 2003. An assessment of the cord blood:maternal blood methylmercury ratio: implications for risk assessment. Environ Health Perspect 111(12):1465–1470, PMID: 12948885, https://doi.org/10.1289/ehp.6187.

Sunyer J, Garcia-Esteban R, Castilla AM, Aurrekoetxea JJ, Iñiguez C, Tardón A, et al. INMA project. 2012. Exposure to second-hand smoke and reproductive outcomes depending on maternal asthma. Eur Respir J 40(2):371–376, PMID: 22323568, https://doi.org/10.1183/09031936.00091411.

Tamayo-Uria I, Maitre L, Thomsen C, Nieuwenhuijsen MJ, Chatzi L, Siroux V, et al. 2019. The early-life exposome: description and patterns in six European countries. Environ Int 123:189–200, PMID: 30530161, https://doi.org/10.1016/j.envint.2018.11.067.

Thayer KA, Heindel JJ, Bucher JR, Gallo MA. 2012. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. Environ Health Perspect 120(6):779–789, PMID: 22296744, https://doi.org/10.1289/ehp.1104597.

Tong X, Ho JMW, Li Z, Lui KH, Kwok TCY, Tsoi KKF, et al. 2019. Prediction model for air particulate matter levels in the households of elderly individuals in Hong Kong. Sci Total Environ 717:135323, PMID: 31839290, https://doi.org/10.1016/j.scitotenv.2019.135323.

Trasande L, Cronk C, Durkin M, Weiss M, Schoeller DA, Gall EA, et al. 2009. Environment and obesity in the National Children's Study. Environ Health Perspect 117(2):159–166, PMID: 19270782, https://doi.org/10.1289/ehp.11839.

Valvi D, Monfort N, Ventura R, Casas M, Casas L, Sunyer J, et al. 2015. Variability and predictors of urinary phthalate metabolites in Spanish pregnant women. Int J Hyg Environ Health 218(2):220–231, PMID: 25558797, https://doi.org/10.1016/j.ijheh.2014.11.003.

van Nunen E, Vermeulen R, Tsai M-Y, Probst-Hensch N, Ineichen A, Davey M, et al. 2017. Land use regression models for ultrafine particles in six European areas. Environ Sci Technol 51(6):3336–3345, PMID: 28244744, https://doi.org/10.1021/acs.est.6b05920.

Voss JD, Masuoka P, Webber BJ, Scher AI, Atkinson RL. 2013. Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States. Int J Obes (Lond) 37(10):1407–1412, PMID: 23357956, https://doi.org/10.1038/ijo.2013.5.

Vrijheid M, Slama R, Robinson O, Chatzi L, Coen M, van den Hazel P, et al. 2014. The Human Early-Life Exposome (HELIX): project rationale and design. Environ Health Perspect 122(6):535–544, PMID: 24610234, https://doi.org/10.1289/ehp.1307204.

Wang M, Beelen R, Bellander T, Birk M, Cesaroni G, Cirach M, et al. 2014. Performance of multi-city land use regression models for nitrogen dioxide and fine particles. Environ Health Perspect 122(8):843–849, PMID: 24787034, https://doi.org/10.1289/ehp.1307271.

Weier J, Herring D. 2000. Measuring Vegetation (NDVI & EVI). https://earthobservatory.nasa.gov/features/MeasuringVegetation [accessed 29 July 2019].

Weyde KV, Krog NH, Oftedal B, Magnus P, White R, Stansfeld S, et al. 2018. A longitudinal study of road traffic noise and body mass index trajectories from birth to 8 years. Epidemiology 29(5):729–738, PMID: 29927819, https://doi.org/10.1097/EDE.0000000000000868.

White IR, Royston P, Wood AM. 2011. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 30(4):377–399, PMID: 21225900, https://doi.org/10.1002/sim.4067.

Wild CP. 2012. The exposome: from concept to utility. Int J Epidemiol 41(1):24–32, PMID: 22296988, https://doi.org/10.1093/ije/dyr236.

Wilding S, Ziauddeen N, Smith D, Roderick P, Alwan NA. 2019. Maternal and early-life area-level characteristics and childhood adiposity: a systematic review. Obes Rev 20(8):1093–1105, PMID: 31034734, https://doi.org/10.1111/obr.12861.

Windham GC, Pinney SM, Sjodin A, Lum R, Jones RS, Needham LL, et al. 2010. Body burdens of brominated flame retardants and other persistent organo-halogenated compounds and their descriptors in US girls. Environ Res 110(3):251–257, PMID: 20129604, https://doi.org/10.1016/j.envres.2010.01.004.

Wolff MS, Anderson HA, Britton JA, Rothman N. 2007. Pharmacokinetic variability and modern epidemiology—the example of dichlorodiphenyltrichloroethane, body mass index, and birth cohort. Cancer Epidemiol Biomarkers Prev 16(10):1925–1930, PMID: 17932339, https://doi.org/10.1158/1055-9965.EPI-07-0394.

Wood AM, White IR, Royston P. 2008. How should variable selection be performed with multiply imputed data? Stat Med 27(17):3227–3246, PMID: 18203127, https://doi.org/10.1002/sim.3177.

Wood SA, Xu F, Armitage JM, Wania F. 2016. Unravelling the relationship between body mass index and polychlorinated biphenyl concentrations using a mechanistic model. Environ Sci Technol 50(18):10055–10064, PMID: 27616073, https://doi.org/10.1021/acs.est.6b01961.

Wright J, Small N, Raynor P, Tuffnell D, Bhopal R, Cameron N, et al. Born in Bradford Scientific Collaborators Group. 2013. Cohort profile: the Born in Bradford multi-ethnic family cohort study. Int J Epidemiol 42(4):978–991, PMID: 23064411, https://doi.org/10.1093/ije/dys112.

Xu X, Yavar Z, Verdin M, Ying Z, Mihai G, Kampfrath T, et al. 2010. Effect of early particulate air pollution exposure on obesity in mice: role of p47phox. Arterioscler Thromb Vasc Biol 30(12):2518–2527, PMID: 20864666, https://doi.org/10.1161/ATVBAHA.110.215350.

Yang Y, Jiang Y, Xu Y, Mzayek F, Levy M. 2018. A cross-sectional study of the influence of neighborhood environment on childhood overweight and obesity: variation by age, gender, and environment characteristics. Prev Med 108:23–28, PMID: 29289640, https://doi.org/10.1016/j.ypmed.2017.12.021.

Yang H, Liu CN, Wolf RM, Ralle M, Dev S, Pierson H, et al. 2019. Obesity is associated with copper elevation in serum and tissues. Metallomics 11(8):1363–1371, PMID: 31249997, https://doi.org/10.1039/c9mt00148d.

Zhang Y, Dong T, Hu W, Wang X, Xu B, Lin Z, et al. 2019. Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: comparison of three statistical models. Environ Int 123:325–336, PMID: 30557812, https://doi.org/10.1016/j.envint.2018.11.076.